

REFERENCE

Donath C, Gräbel E, Baier D, *et al.* (2011). Alcohol consumption and binge drinking in adolescents: comparison of different migration backgrounds and rural vs. urban residence – a representative study. *BMC Public Health* 11:84.

O1.4

ADAPTATION OF THE ALCOHOL EXPECTANCY QUESTIONNAIRE (AEQ-A): FOR USE AMONG ADOLESCENTS IN PORTUGAL

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Introduction. Previous studies have suggested that alcohol expectancies influence both the behavioural effects and different consumption patterns and can be modified via preventative efforts (Rönback *et al.*, 1999; Barroso, 2009). Expectancies are formed early, even prior to personal experiences of alcohol consumption through social learning processes during childhood and adolescence (Miller *et al.*, 1990; Goldman *et al.*, 1991; Perez-Aranibar *et al.*, 2005).

Objective. The aim of this study was to translate and adapt the Alcohol Expectancy Questionnaire – Adolescent Form (AEQ-A: Goldman *et al.*, 1982) for usage within the Portuguese adolescent population.

Methods. This process of adaptation included three studies with adolescents ($n = 654, 205$ and 212). Internal consistency, construct validity and concurrent validity were assessed. The three psychometric studies resulted in the development of a Scale of Positive Alcohol Expectancies (EEPA-A/AEQ-A).

Results. This new version of the AEQ-A revealed a good internal consistency (Cronbach's $\alpha = 0.94$). Factor analysis (KMO = 0.890; Bartlett's test = 4419.729; $P = 0.000$) with the Varimax orthogonal rotation of the 49 remaining items revealed four factors with eigenvalues ≥ 1 , explaining 40.81% of the total variance: Factor I. Facilitator of interpersonal relationships; Factor II. Stimulation and tension reduction; Factor III. Escape from negative emotional states; Factor IV. Change in social behavior and sexual arousal ($\alpha = 0.82-0.85$). The factor associated with the modification of social behavior and sexual activation was significantly higher in adolescents who had consumed alcohol and had experienced intoxication ($P = 0.000$). The escape from negative emotional states factor was significantly higher in adolescents who had experienced intoxication ($P = 0.034$).

Conclusions. This solution and its interpretation presented herein therefore incorporate much of the previously established knowledge in the expectancies literature. It contains 49 Likert-type items, with good reliability as well as construct validity. This scale displays sensitivity to previous alcohol consumption even in cases of experimental consumption, and is useful for the behavioral research of alcohol consumption amongst Portuguese adolescents.

O1.5

THE IMPACT OF TEMPERAMENT, ATTENTION DEFICIT HYPERACTIVITY DISORDER AND PSYCHOSOCIAL FACTORS ON SUBSTANCE USE AND THE MOTIVATION TO CONSUME IN YOUNG ADULT MALES

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The consumption of alcohol, nicotine and illicit drugs is common among adolescents and young adults, and poses serious health risks.

Objective. The association between dimensions of temperament, attention deficit hyperactivity disorder (ADHD), psychosocial factors and the use of alcohol, nicotine and illicit drugs.

Method. We investigated a representative sample of 18-year-old males ($n = 3284$) using questionnaires as well as biological markers. Due to conscription to the military service, all young men in Austria have to undergo an examination of their health status. This physical and psychological examination enabled us to investigate a representative sample of young men, independent of background, social status and education. Therefore, we could collect data regarding the prevalence of the use of alcohol, nicotine and illicit drug use, ADHD symptomatology and further aspects. We assessed different psychosocial factors such as life satisfaction, family history of

drinking and smoking, leisure behaviour as well as onset, patterns and motivation of substance use. To evaluate alcohol and illicit drug use and misuse, we collected blood and urine samples, to test for smoking we measured carbon monoxide in exhaled air and we also collected some biological markers (e.g. body mass index, waist circumference).

Questionnaires. We used the TEMPS-M for temperament (according to Akiskal), the ADHD checklist according to DSM IV as well as the Wender Utah Rating Scale (WURS) were used to assess the symptomatology of ADHD, the CAGE questionnaire to test for alcohol misuse and dependence and the Fagerstrom questionnaire to test for nicotine dependence. Data concerning the prevalence of ADHD symptomatology, psychosocial factors and temperament dimensions (according to Akiskal *et al.*) in connection with alcohol, nicotine and substance use as well as the motivation to consume will be presented. Furthermore, we will show how our findings could contribute to the development of more specific and need orientated prevention strategies of high-risk groups.

O1.6

INPATIENT DETOXIFICATION AND LAW ENFORCEMENT COSTS RELATED TO ACUTE DRINKING EVENT

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Aims. Assessment of inpatient alcohol detoxification and related law enforcement costs size and structure.

Methods. Retrospectively designed, bottom-up, case-control trial conducted from societal perspective with a chosen time horizon was 1 year.

Results. In 2009, 379 patients were admitted 952 times to the regional Psychiatry Clinic, due to heavy drinking event. Number of admissions was 2.49 ± 2.36 male and 2.67 ± 3.41 female. Costs evidenced included drug acquisition, hospital admission (consultations included), treatment costs, psychotherapy techniques, consumables and law enforcement. Overall, the amount spent for inpatient detoxification ranged per patient from €8.62 to €965.81. Observed cohort of patients imposed €12,662.94 of direct medical costs in a given year 2009 or average €32.27 per male and €36.07 per female patient. Law enforcement costs were calculated at €11,028.27 for those patients who were reported for criminal offenses (81 of them or 21.37%) or €136.15 per patient prosecuted. Total financial resources spent were €22,709.68. Based on national prevalence data, we estimated that our country needs at least €9,784,011 of budget allocation to cover these expenses.

Conclusions. Acquired data exhibit substantial economic and work load of local hospitals with acute detoxification and its consequences. This data would provide policy-makers with a firm ground for decision-making on better funding of treatment programmes, including founding network of detoxification facilities.

FREE ORAL COMMUNICATIONS 2: ALCOHOL AND LIVER—CLINICAL RESEARCH

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O2.1

RAPID DECLINE OF LIVER STIFFNESS WITH ALCOHOL WITHDRAWAL IN HEAVY DRINKERS

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Background and aims. Measurement of liver stiffness using real-time elastography appears as a promising tool to evaluate the severity of chronic liver diseases. Previous studies in patients with alcoholic liver disease have suggested that fibrosis was the only histological parameter to influence liver stiffness. To challenge this hypothesis, we have prospectively tested the short-term impact of alcohol withdrawal on liver stiffness value.

Methods. All patients hospitalized for alcohol withdrawal in our Liver Unit between September 2008 and December 2010 had a liver stiffness

determination (using a FibroScan® device) at entry (D0) and 7 days after alcohol withdrawal (D7). Stiffness values were compared using non-parametric test for paired-values. We compared (i) the 10 measures performed at D0 and at D7 for each patient; (ii) the variation of the median result of all patients (using Wilcoxon test in both cases).

Results. A total of 138 patients were included in the study [median alcohol consumption: 150 g/day (range: 40–400); hepatitis C: $n = 22$ (15.9%); cirrhosis: $n = 29$ (21.0%)]. From D0 to D7, the liver stiffness decreased significantly in 61 patients (44.2%) and increased significantly in 18 (13.0%). Considering all patients, median liver stiffness value decreased from 7.25 to kPa ($P < 0.001$). The stage of fibrosis indicated by liver stiffness changed in 47 patients between D0 and D7 (decrease in 33 and increase in 14).

Conclusion. Liver stiffness decreases significantly in nearly half of alcoholic patients after only 7 days of abstinence. This result strongly suggests that non-fibrotic lesions (such as inflammatory ones) may influence liver stiffness. From a practical point of view, it also shows that variation in alcohol consumption must be taken into account for the interpretation of liver stiffness value.

O2.2

IS HISTOLOGY THE 'ADEQUATE' GOLD STANDARD TO VALIDATE THE ASSESSMENT OF ALCOHOLIC LIVER FIBROSIS BY TRANSIENT ELASTOGRAPHY (FIBROSCAN)?

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Background. Measurement of liver stiffness (LS) by transient elastography (Fibroscan, FS) is a novel noninvasive approach to assess liver fibrosis with a high diagnostic accuracy. However, accuracy may be even higher since histology served as gold standard in all previous LS studies although its sample error may reach up to 30%. Consequently, we here determined the AUROC for FS to detect liver cirrhosis using a combination of histology and definite clinical signs of cirrhosis as obtained by ultrasound or gastroscopy in patients with alcoholic liver disease (ALD).

Method. LS was measured in 90 patients with histologically confirmed ALD. An LS of >8 kPa was considered as cut-off for F3/4 fibrosis. Patients with significant steatohepatitis (GOT > 100 U/l) were excluded since inflammation increases LS irrespective of fibrosis. We finally compared FS-results with the combination of the histological fibrosis score (Kleiner) plus additional clinical information (macronodular surface or collateral circuits in ultrasound imaging, varices in upper GI endoscopy).

Results. A total of 77 patients were scored correctly by FS using the Kleiner score as gold standard. Of 39 patients, 4 (10.2%) with histological F3/4 fibrosis had an LS of <8 kPa, but no clinical signs of liver cirrhosis. Of 51 patients, 9 (17.6%) with histological F0-2 fibrosis had an LS of >8 kPa, 2 of them had definite clinical signs of liver cirrhosis. Two more patients had an enlarged spleen (>12 cm) suggesting portal hypertension. Thus, in 8 of 90 patients (8.8%), additional clinical information was able to resolve the divergence between histology and fibroscan. AUROC for the detection of F3/4 fibrosis by FS increased from 0.923 to 0.985 when histology in combination with clinical signs of cirrhosis was used as gold standard.

Conclusion. FS results should be compared against a combination of histology and clinical information to minimize the effects of sampling error in liver biopsy. Using this as the new gold standard, FS reaches an AUROC of 0.98 in F3/4 diagnosis.

O2.3

ROLE OF INTESTINAL PERMEABILITY AND INFLAMMATION IN THE BIOLOGICAL AND BEHAVIORAL CONTROL OF ALCOHOL-DEPENDENT SUBJECTS

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Aims. Alcohol dependence is commonly investigated in relation to modification of various neurotransmitters in brain. Our hypothesis is that the development of alcohol dependence could also involve more peripheral mechanisms and especially gut-brain interactions. Our first goal was to test whether intestinal permeability, lipopolysaccharides (LPS) and inflammatory cytokines are increased in alcohol-dependent subjects and recover after withdrawal. To explore the possible role of gut-brain axis in alcoholism, our

second goal was to test correlations between the biological and the behavioral variables that are known to play a central role in alcohol dependence, such as depression, anxiety, alcohol craving and selective attention.

Methods. Forty alcohol-dependent subjects hospitalized for detoxification program were tested both at onset (T1) and at the end (T2) of withdrawal and compared for biological and behavioral markers with a control group. Participants were evaluated for gut permeability, LPS, systemic inflammation (TNF α , IL-6, IL-10, and hsCRP) and stress (Cortisol) and for depression (BDI), anxiety (STAI), alcohol craving (OCDS) and selective attention (BAWL).

Results. Intestinal permeability and LPS that were largely increased in alcohol-dependent subjects at T1 recovered completely at T2. A low-grade inflammation was observed at T1 and recovered partially after withdrawal in parallel with the psychological variables. We found that pro-inflammatory markers were positively correlated with depression and craving. The anti-inflammatory cytokine IL-10 was negatively correlated with depression and craving.

Conclusion. Leaky gut-induced inflammation is correlated to emotions and craving for alcohol. We can therefore consider that gut-brain axis may play a significant role in the development of alcoholic pathology. IL-10 could be a protective factor in relation to emotional disturbances and relapse probability. Moreover, recent animal and human studies have shown that chronic alcohol consumption altered gut microbiota. An interesting perspective would be to test pro- or prebiotics that are known to improve the composition of gut microbiota and therefore restore the gut barrier to reduce inflammation, depression and craving to help patients to remain abstinent.

O2.4

THE LOSS OF METABOLIC CONTROL ON ALCOHOL DRINKING IN HEAVILY DRINKING ALCOHOLICS

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Background. Most physiological studies of alcoholism consider ethanol as a pharmacological agent rather than a nutrient. We conducted two studies to assess potent metabolic and endocrine factors of alcohol and nutrient intake regulation in alcoholic subjects and a possible role of a disruption of energy balance for the development of alcoholism.

Methods and results. Study 1 consists of quantitative anamneses of eating and drinking habits among 97 alcoholics. The population was split around a median alcohol intake value of 12.5 kcal/kg/day. 'Low alcohol' drinking alcoholics had high BMI and fat mass (FM) and alcohol intake was compensated for by a decrease in non-alcoholic intake. 'High alcohol' drinking alcoholics had low BMI and FM and the total intake was largely above norms. In Study 2, 22 alcoholic inpatients submitted on Day 2, 5 and 16 of abstinence to diet anamneses, calorimetry and blood sampling for the measurement of biomarkers reflecting metabolism and satiety regulation were compared with 19 matched controls. We observed increased cortisol, leptin and PYY plasma levels and decreased plasma ghrelin that might explain the observed decrease in non-alcoholic intake. However, both alcoholic and non-alcoholic intake correlated positively with basal metabolism and negatively with leptin and leptin/BMI.

Conclusion. Below 12.5kcal/kg/day alcohol intake is compensated for by a decrease in nutrient intake, probably due to changes in metabolic and satiety factors. Above 12.5 kcal/kg/day alcohol intake accelerates metabolism and decreases fat mass and leptin levels, and the total intake largely exceeds norms. A dual model for regulation of energy intake in alcoholics is suggested.

O2.5

SPECIFICITY OF MACROSTRUCTURAL ABNORMALITIES IN KORSAKOFF'S SYNDROME COMPARED WITH UNCOMPLICATED ALCOHOLISM

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While neuropathological studies initially reported that shrinkage of the thalamic nuclei and mammillary bodies characterized Korsakoff's syndrome (KS), neuroimaging investigations revealed widespread cerebral damage including notably brain abnormalities in the frontal cortex, hippocampus and cerebellum. Reduced volume in these brain regions has also been shown in alcoholics without ostensible neurological complications (AL). The goals of the present study were therefore to identify (i) brain volume decrease related to chronic alcohol consumption and common to both AL and KS, and (ii) regions

specifically damaged in KS compared with AL. To this end, we conducted a whole brain analysis of gray and white matter volume in KS, AL and control subjects from T1-weighted MRI scan obtained in each participant. A conjunction analysis in AL and SK compared with control subjects indicated decreased gray matter volume bilaterally in the prefrontal cortex extending to the parietal lobe, and in the insula, hippocampal formation, caudate, thalami, hypothalami and cerebellum. Gray matter volumes were reduced in KS compared with both controls and AL bilaterally in the thalami, hypothalami (mammillary bodies) and left insula. There were graded effects of volume deficits in the thalami, mammillary bodies and insula from mild or moderate in AL to severe in KS. Regarding white matter, the conjunction analysis showed lower volume in both AL and SK compared with controls bilaterally in the fornix, stria terminalis, cingulate bundle and corona radiata, and in the corpus callosum and mesencephalic fibers. Compared with AL, a greater decrease in white matter volume was found in KS bilaterally in the genu of the corpus callosum with graded effects of volume deficit in AL and KS. Our results indicate therefore that AL and KS present a common pattern of widespread alcoholism-related volume deficits affecting especially the limbic and frontocerebellar networks. In agreement with the continuity theory, the specificity of gray and white matter abnormalities in KS seems to lie in the exacerbation of alcoholism-related alterations in the thalami, mammillary bodies, insula and genu of the corpus callosum.

O2.6

CYTOCHROME P450 2E1 AS AN IMPORTANT FACTOR OF HEPATIC STEATOSIS AND FIBROSIS IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Background. Although the pathogenesis of alcoholic liver disease (ALD) is still unclear, there is increasing evidence of the involvement of cytochrome P-4502E1 (CYP2E1) in its progression, since the inhibition of CYP2E1 in animal experiments prevents ALD. In addition, CYP2E1 seems also responsible for the generation of carcinogenic DNA lesions in both ALD and NAFLD. The purpose of this study was to further investigate the role of CYP2E1 in hepatic steatosis, fibrosis and carcinogenesis in human livers.

Methods. The degree of fat, fibrosis and CYP2E1 induction was determined in liver biopsies from 60 patients with various stages of ALD and 39 patients with NAFLD. Carcinogenic DNA lesions such as exocyclic etheno-DNA adducts (edA) and 8-OH deoxyguanine (8-OHdG) were also measured.

Results. CYP2E1 induction ($P < 0.01$), steatosis ($P < 0.01$) and fibrosis ($P < 0.01$) were more pronounced in the livers of patients with ALD when compared with NAFLD. A significant correlation was found between CYP2E1 and hepatic steatosis as well as fibrosis ($P < 0.01$). The induction of CYP2E1 was associated with the generation of highly carcinogenic etheno DNA adducts ($P < 0.01$), but not with 8-OHdG.

Discussion and conclusion. The data emphasize the causal role of CYP2E1 in the progression of ALD. They further demonstrate that CYP2E1 is induced in fatty livers regardless of its cause resulting in the generation of carcinogenic DNA lesions. Thus, fatty liver may be a condition predisposing to cancer and additional alcohol intake may increase cancer risk.

FREE ORAL COMMUNICATIONS 3: ALCOHOL–BRAIN: FROM BASIC TO CLINICAL RESEARCH

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O3.1

COMPARISON OF THE EFFECT OF THE GABA(B) RECEPTOR AGONIST, BACLOFEN, ON ALCOHOL SELF-ADMINISTRATION IN THREE DIFFERENT LINES OF ALCOHOL-PREFERRING RATS

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Treatment with the GABA(B) receptor agonist, baclofen (BAC), has been reported to suppress multiple alcohol-related behaviors in rats and mice. The

present study compared the effect of BAC on alcohol self-administration (S-A) in three lines of selectively bred, alcohol-preferring rats: Indiana (P), Sardinian (sP) and Alko Alcohol (AA) alcohol-preferring rats. To this end, rats of each line were trained to lever-respond on a Fixed Ratio 4 (FR4) to orally self-administer alcohol (15%, v/v) in daily 30-min sessions. Once responding stabilized, rats were exposed to a sequence of experiments testing BAC (0, 1, 1.7 and 3 mg/kg; i.p.) on FR4 and progressive ratio (PR) schedules of reinforcement. Specificity was assessed testing BAC on food-maintained responding. The rank of order of alcohol-reinforcing properties was: $P > sP > AA$ rats. BAC was more potent and effective in suppressing alcohol S-A in P than sP and AA rats. Reduction in number of lever-responses, amount of self-administered alcohol and breakpoint for alcohol in P rats treated with 1.7 and 3 mg/kg BAC averaged approximately 50 and 80%, respectively. BAC-treated sP rats displayed intermediate values between those of P and AA rats. Only 3 mg/kg BAC reduced responding for food; this effect was common to all three rat lines. These results suggest that: (a) the strength of alcohol reinforcing properties differs among P, sP and AA rats; (b) alcohol-reinforcing properties in P, sP and AA rats are differentially sensitive to BAC; (c) the heterogeneity in sensitivity to BAC in P, sP and AA rats may resemble the differential sensitivity to pharmacotherapies among typologies of human alcoholics; (d) the GABA(B) receptor is likely part of the neural substrate mediating alcohol-reinforcing properties [see also the companion paper on GS39783 (Maccioni *et al.*, this meeting)]. (This study was supported by *Compagnia di San Paolo*, Turin, Italy. P.M. is awardee of a fellowship from *Regione Autonoma della Sardegna*, PO Sardegna FSE 2007-2013, L.R. 7/2007.)

O3.2

COMPARISON OF THE EFFECT OF THE POSITIVE ALLOSTERIC MODULATOR OF THE GABA(B) RECEPTOR, GS39783, ON ALCOHOL SELF-ADMINISTRATION IN THREE DIFFERENT LINES OF ALCOHOL-PREFERRING RATS

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Treatment with positive allosteric modulators of the GABA(B) receptor, including GS39783 (GS), has been found to reduce alcohol self-administration (S-A) in rats. The present study compared the effect of GS on alcohol S-A in three lines of selectively bred, alcohol-preferring rats: Indiana (P), Sardinian (sP) and Alko Alcohol (AA) alcohol-preferring rats. To this end, rats of each line were trained to lever-respond on a Fixed Ratio 4 (FR4) to orally self-administer alcohol (15%, v/v) in daily 30-min sessions. Once responding stabilized, rats were exposed to a sequence of experiments testing GS (0, 25, 50, and 100 mg/kg; i.g.) on FR4 and progressive ratio (PR) schedules of reinforcement. Specificity was assessed testing GS on food-maintained responding. The rank of order of alcohol-reinforcing properties was: $P > sP > AA$ rats. GS was more potent and effective in suppressing alcohol S-A in P than sP and AA rats. The number of lever responses, amount of self-administered alcohol and breakpoint for alcohol were more than halved at each GS dose in P rats. GS administration dose-dependently reduced alcohol S-A under both schedules in sP rats. Conversely, GS reduced alcohol S-A under FR4, but not PR, schedule in AA rats. No dose of GS altered responding for food in any rat line. These results suggest that: (a) the strength of alcohol-reinforcing properties differs among P, sP and AA rats; (b) alcohol-reinforcing properties in P, sP and AA rats are differentially sensitive to GS; (c) the heterogeneity in sensitivity to GS in P, sP and AA rats may resemble the differential sensitivity to pharmacotherapies among typologies of human alcoholics; (d) the GABA(B) receptor is likely part of the neural substrate mediating alcohol-reinforcing properties [see also the companion paper on baclofen (Maccioni *et al.*, this meeting)]. (this study was supported by *Compagnia di San Paolo*, Turin, Italy. P.M. is awardee of a fellowship from *Regione Autonoma della Sardegna*, PO Sardegna FSE 2007-2013, L.R. 7/2007.)

O3.3

OXIDATIVE THEORY OF STRUCTURE-SPECIFIC ACTION OF ALCOHOL IN BRAIN

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When consuming, ethanol easily passes the blood–brain barrier and reaches all structures and cells in the brain, but influences them differently. What are